Claims

1. A liposome comprising a first adjuvant and at least one second adjuvant, which is different from the first adjuvant, and at least one therapeutic agent.

2. A mixture of liposomes comprising a first liposome comprising at least a first adjuvant and at least one therapeutic agent and at least a second liposome comprising at least a second adjuvant, which is different from the first adjuvant.

3. A mixture of liposomes comprising a first liposome comprising at least a first adjuvant, a second liposome comprising at least one therapeutic agent and at least a third liposome comprising at least a second adjuvant, which is different from the first adjuvant.

4. A mixture of liposomes comprising a first liposome comprising at least a first adjuvant, a second liposome comprising at least one therapeutic agent and a liquid medium comprising at least a second adjuvant, which is different from the first adjuvant.

5. A liposomal composition comprising a liposome comprising a first adjuvant and at least one therapeutic agent and a liquid medium comprising at least a second adjuvant, which is different from the first adjuvant.

6. The liposome or the mixture of liposomes of one of claims 1 to 3, wherein the liposome(s) is(are) comprised in a liquid medium.

7. The liposome, the mixture of liposomes or the liposomal composition of one of claims 4 to 6, wherein the liquid medium is selected from the group consisting of H_20, aqueous salt solution, and buffer solution.

8. The liposome, the mixture of liposomes or the liposomal composition of any of claims 1 to 7, comprising at least one further component selected from the group consisting of an adjuvant, an additive, and an auxiliary substance.

9. The liposome, the mixture of liposomes or the liposomal composition of any of claims 1

to 8, wherein the lipids of the liposome comprise cholesterol and at least one negatively charged lipid.

10. The liposome, the mixture of liposomes or the liposomal composition of claim 9, wherein the negatively charged lipid comprised in the liposome is selected from the group consisting of phosphatidylserine (PS), phosphatidylglycerol (PG) and phosphatidic acid (PA).

11. The liposome, the mixture of liposomes or the liposomal composition of any of claims 1 to 10, wherein the liposome comprises cholesterol and at least two components selected from the group consisting of PS, PG and PE.

12. The liposome, the mixture of liposomes or the liposomal composition of claim 11, wherein the liposome, comprises in relation to the total molar lipid composition of the liposome:

a) between 20 mol% and 60 mol% CH; and

b) between 20 mol% and 50 mol% PS;
between 20 mol% and 50 mol% PG and
between 20 mol% and 50 mol% PE, respectively.

13. The liposome, the mixture of liposomes or the liposomal composition of any of claims 9 to 12, wherein between one and three components selected from the group consisting of CH, PS, PG and PE is (are) present in relation to the total molar lipid composition of the liposome at a molar ratio of between 30 mol% and 36 mol%.

14. The liposome, the mixture of liposomes or the liposomal composition of any of claims 9 to 13, wherein the remaining lipid of the liposome is selected from the group consisting of glycerides, glycerophospholipides, glycerophosphinolipids, glycerophosphonolipids, sulfolipids, sphingolipids, phospholipids, isoprenolides, steroids, stearines, steroles and carbohydrate containing lipids.

15. The liposome, the mixture of liposomes or the liposomal composition of claim 14, wherein said remaining phospholipid is phosphatidylcholine (PC) or PE.

16. The liposome, the mixture of liposomes or the liposomal composition of one of claims 11 to 15, wherein the lipids of the liposome essentially consist of CH, PS, and PG; CH, PS and PE; CH, PG, and PE; or CH, PG, PS, and PE.

17. The liposome, the mixture of liposomes or the liposomal composition of one of claims 1 to 16, wherein the therapeutic agent is selected from the group consisting of a drug and an antigen.

18. The liposome, the mixture of liposomes or the liposomal composition of claim 17, wherein the antigen is selected from the group of antigens consisting of a tumor antigen, a viral antigen, a fungal antigen, a bacterial antigen, an autoimmune antigen or an allergen.

19. The liposome, the mixture of liposomes or the liposomal composition of claim 18, wherein the tumor antigen is selected from the group consisting of T-cell-defined cancer-associated antigens belonging to unique gene products of mutated or recombined cellular genes, in particular cyclin-dependent kinase 4 (CDK4), $p15^{Ink4b}$, p53, AFP, ß-catenin, caspase 8, p53, $p21^{Ras}$ mutations, Bcr-abl fusion product, MUM-1 MUM-2, MUM-3, ELF2M, HSP70-2M, HST-2, KIAA0205, RAGE, myosin/m, 707-AP, CDC27/m, ETV6/AML, TEL/Aml1, Dekcain, LDLR/FUT, Pml-RARα, TEL/AMLI; Cancer-testis (CT) antigens, in particular NY-ESO-1, members of the MAGE-family (MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A6 MAGE-10, MAGE-12), BAGE, DAM-6, DAM-10, members of the GAGE-family (GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7B, GAGE-8), NA-88A, CAG-3, RCC-associated antigen G250; Tumor virus antigens, in particular human papilloma virus (HPV)-derived E6 E7 oncoproteins, Epstein Barr virus EBNA2-6, LMP-1, LMP-2; overexpressed or tissue-specific differentiation antigens, in particular gp77, gp100, MART-1/Melan-A, p53, tyrosinase, tyrosinase-related protein (TRP-1 and TPR-2), PSA, PSM, MC1R; widely expressed antigens, in particular ART4, CAMEL, CEA, CypB, HER2/neu, hTERT, hTRT, iCE, Muc1, Muc2, PRAME RU1, RU2, SART-1, SART-2, SART-3, and WT1; and fragments and derivatives thereof.

20. The liposome, the mixture of liposomes or the liposomal composition of claim 18, wherein the viral antigen is derived from a virus selected from the group of virus consisting of Retroviridae, in particular HIV-1 and HIV-LP; Picornaviridae, in particular

polio virus and hepatitis A virus; enterovirus, in particular human coxsackie virus, rhinovirus, echovirus; Calciviridae, in particular strains that cause gastroenteritis; Togaviridae, in particular equine encephalitis virus and rubella virus; Flaviridae, in particular dengue virus, encephalitis virus and yellow fever virus; Coronaviridae, in particular coronavirus; Rhabdoviridae, in particular vesicular stomatitis virus and rabies virus; Filoviridae, in particular Ebola virus or and Marburg virus; Paramyxoviridae, in particular parainfluenza virus, mumps virus, measles virus and respiratory syncytical virus; Orthomyxoviridae, in particular influenza virus; Bungaviridae, in particular Hantaan virus, bunga virus, phlebovirus and Nairo virus; Arena viridae, in particular hemorrhagic fever virus; Reoviridae, in particular reovirus, orbivirus and rotavirus; Birnaviridae; Hepadnaviridae, in particular Hepatitis B virus; Parvovirida, in particular parvovirus; Papovaviridae, in particular papilloma virus, simian virus-40 (SV40) and polyoma virus; Adenoviridae; Herpesviridae, in particular herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes virus; Poxviridae, in particular variola virus, vaccinia virus and pox virus; and Iridoviridae, in particular African swine fever virus; and Hepatitis C.

21. The liposome, the mixture of liposomes or the liposomal composition of claim 18, wherein the fungal antigen is derived from a fungus selected from the group consisting of *Cryptococcus* species, in particular *Cryptococcus neoformans*, *Histoplasma* species, in particular *Histoplasma capsulatum*, *Coccidioides* species, in particular *Coccidioides immitis*, *Blastomyces* species, in particular Blastomyces *dermatitidis*, *Chlamydia* species, in particular *Chlamydia trachomatis*, and *Candida* species, in particular *Candida albicans*.

22. The liposome, the mixture of liposomes or the liposomal composition of claim 18, wherein the bacterial antigen is derived from a bacterium selected from the group consisting of Helicobacter species, in particular *Helicobacter pyloris*; Borelia species, in particular *Borelia burgdorferi*; Legionella species, in particular *Legionella pneumophilia*; Mycobacteria species, in particular *M. tuberculosis*, *M. avium*, *M. intracellulare*, *M. kansasii*, *M. gordonae*; Staphylococcus species, in particular *Staphylococcus aureus*; Neisseria species, in particular *N. gonorrhoeae, N. meningitidis*; Listeria species, in particular *Listeria monocytogenes*; Streptococcus species, in particular *S. pyogenes*, *S. agalactiae*; *S. faecalis*; *S. bovis*, *S. pneumoniae*; anaerobic Streptococcus species;

pathogenic Campylobacter species; Enterococcus species; Haemophilus species, in particular *Haemophilus influenzae*; Bacillus species, in particular *Bacillus anthracis*; Corynebacterium species, in particular *Corynebacterium diphtheriae*; Erysipelothrix species, in particular *Erysipelothrix rhusiopathiae*; Clostridium species, in particular *C. perfringens*, *C. tetani*; Enterobacter species, in particular *Enterobacter aerogenes*, Klebsiella species, in particular *Klebsiella pneumoniae*, Pasturella species, in particular *Pasturella multocida*, Bacteroides species; Fusobacterium species, in particular *Fusobacterium nucleatum*; Streptobacillus species, in particular *Streptobacillus moniliformis*; Treponema species, in particular *Treponema pertenue*; Leptospira; pathogenic Escherichia species; and Actinomyces species, in particular *Actinomyces israelli*.

23. The liposome, the mixture of liposomes or the liposomal composition of one of claims 1 to 22, wherein the first and the second adjuvant is selected from the group consisting of unmethylated DNA, in particular unmethylated DNA comprising CpG dinucleotides (CpG motif), in particular CpG ODN with phosphorothioate (PTO) backbone (CpG PTO ODN) or phosphodiester (PO) backbone (CpG PO ODN); bacterial products from the outer membrane of Gram-negative bacteria, in particular monophosphoryl lipid A (MPLA), lipopolysaccharides (LPS), muramyl dipeptides and derivatives thereof; synthetic lipopeptide derivatives, in particular Pam_3Cys; lipoarabinomannan; peptidoglycan; zymosan; heat shock proteins (HSP), in particular HSP 70; dsRNA and synthetic derivatives thereof, in particular Poly I:poly C; polycationic peptides, in particular poly-L-arginine; taxol; fibronectin; flagellin; imidazoquinoline; cytokines with adjuvant activity, in particular GM-CSF, interleukin- (IL-)2, IL-6, IL-7, IL-18, type I and II, interferons, in particular interferon-gamma, TNF-alpha; 25-dihydroxyvitamin D3 (calcitriol); synthetic oligopeptides, in particular MHCII-presented peptides; gel-like precipitates of aluminum hydroxide (alum).

24. The liposome, the mixture of liposomes or the liposomal composition of claim 23, wherein the first and the second adjuvant stimulate different receptors and/or pathways within cells of the immune system.

25. The liposome, the mixture of liposomes or the liposomal composition of claim 24, wherein the first and the second adjuvant stimulate at least two receptors selected from

the group consisting of type I cytokine receptors, type II cytokine receptors for, TNF receptors; and vitamin D receptor acting as transcription factor; and the Toll-like receptors 1 (TLR-1), TLR-2, TLR 3, TLR4, TLR5, TLR-6, TLR7 and TLR9.

26. The liposome, the mixture of liposomes or the liposomal composition of claim 25, wherein the first and the second adjuvant, which primarily stimulate different receptors are selected for:

a) type I cytokine receptors from the group consisting of GM-CSF, IL-2, IL-6 and IL-7;

b) type II cytokine receptors from the group consisting of IFN-α/β and IFN-γ;

c) TNF receptors from the group consisting of TNF-α and CD40 ligand;

d) vitamin D receptor from the group consisting of calcitriol;

e) TLR-1 from the group consisting of tri-acyl lipopeptides from bacteria and mycobacteria and soluble factors from Neisseria meningitides;

f) TLR-2 from the group consisting of lipopeptides, in particular Pam_3Cys, lipoarabinomannan from mycobacteria, peptidoglycan, zymosan and heat shock proteins (HSPs), in particular HSP70, ; lipoteichoic acid from gram-positive bacteria, phenol-soluble modulin from Staphylococcus species., in particular *Staphylococcus epidermidis*, glycoinositolphospholipids from Trypanosoma species, in particular *Trypanosoma cruzi*, glycolipids from Treponema maltophilum, porins from Neisseria, atyptical LPS from Leptospira species, in particular *Leptospira interrogans* and Porphyromonas species, in particular *Porphyromonas gingivalis*;

g) TLR-3 from the group consisting of viral double-stranded RNA and poly dI:dC;

h) TLR-4 from the group consisting of LPS from gram-negative bacteria and its derivatives, in particular monophosphoryl lipid (MPLA), HSPs in particular HSP60 and HSP70, Taxol, fusion proteins of RSV, envelope protein of MMTV, fibronectin and fragments thereof, oligosaccharides of hyaluronic acid, polysaccharide fragments of heparan sulfate and fibrinogen;

i) TLR-5 from the group consisting of bacterial flagellin;

j) TLR-6 from the group consisting of di-acyl lipopeptides from mycoplasma;

k) TLR-7 from the group consisting of imidazoquinoline, loxoribine and bropirimine; and

l) TLR-9 from the group consisting of unmethylated DNA, in particular CpG-DNA; unmethylated phosphorothioate (PTO) oligonucleotides, in particular CpG-PTO

oligonucleotides.

27. The liposome, the mixture of liposomes or the liposomal composition of one of claims 1 to 26, wherein a targeting moiety is attached to the liposome.

28. A method for producing the liposome, the mixture of liposomes or the liposomal composition of one of claims 1 to 27, wherein the method of producing the liposome, comprises the steps of:

a) forming a suspension of at least one lipid, one or more therapeutic agent and optionally a first and/or a second adjuvant in a liquid medium and

b) homogenizing the suspension.

29. A liposome produced by the method of claim 28.

30. Use of a liposome, the mixture of liposomes or the liposomal composition of one of claims 1 to 26 or claim 28 for the production of a medicament for the prevention or therapy of proliferative diseases, infectious diseases, vascular diseases, rheumatoid diseases, inflammatory diseases, immune diseases, and allergies.

31. The use of claim 30, wherein the proliferative disease is selected from the group consisting of carcinomas of the gastrointestinal or colorectal tract, liver, pancreas, kidney, bladder, prostate, endometrium, ovary, testes, melanoma, dysplastic oral mucosa, invasive oral cancers, small cell and non-small cell lung carcinomas, hormone-dependent breast cancers, hormone independent breast cancers, transitional and squamous cell cancers, neurological malignancies including neuroblastoma, gliomas, astrocytomas, osteosarcomas, soft tissue sarcomas, hemangioamas, endocrinological tumors, hematologic neoplasias including leukemias, lymphomas, and other myeloproliferative and lymphoproliferative diseases, carcinomas in situ, hyperplastic lesions, adenomas, fibromas, histiocytosis, chronic inflammatory proliferative diseases, vascular proliferative diseases and virus-induced proliferative diseases.

32. The use of claims 30 or 31, wherein an adjuvant and/or a cytokine is (are) administered prior, simultaneously or after administration of the liposome or liposomal composition.

33. The use of claim 32, wherein the adjuvant is selected from the group of adjuvants consisting of unmethylated DNA, in particular unmethylated DNA comprising CpG dinucleotides, in particular CpG PTO ODN or CpG PO ODN; alum; bacterial products from the outer membrane of Gram-negative bacteria, in particular MPLA, LPS, muramyl dipeptides and derivatives thereof; synthetic lipopeptide derivatives, in particular Pam_3Cys; lipoarabinomannan; peptidoglycan; zymosan; HSP, in particular HSP 70; dsRNA and synthetic derivatives thereof, in particular Poly I:poly C; polycationic peptides, in particular poly-L-arginine; taxol; fibronectin; flagellin; imidazoquinoline; cytokines with adjuvant activity, in particular GM-CSF, IL-2, IL-6, IL-7, IL-18, type I and II, interferons, in particular interferon-gamma, TNF-alpha; oil in water emulsions, in particular MF59 consisting of squalene; Tween 80 and Span 85 and QS-21, non-ionic block polymers, in particular Poloxamer 401, saponins and derivatives thereof; polyphosphazene; BAY R1005, calcitriol; DHEA; [MDP(Gln)-OMe; murapalmitine; polymers of lactic and/or glycolic acid; polymethyl methacrylate; sorbitan trioleate; squalane; stearyl tyrosine; squalene; theramide, synthetic oligopeptides, in particular peptides presented by MHC-class II.